Journal of the American College of Cardiology Vol. 46, No. 12, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.02.096

FOCUS ISSUE: CARDIAC RESYNCHRONIZATION THERAPY

Diastolic Asynchrony Is More Frequent Than Systolic Asynchrony in Dilated Cardiomyopathy and Is Less Improved by Cardiac Resynchronization Therapy

Iris Schuster, MD,* Gilbert Habib, MD, FACC,* Christophe Jego, MD,* Franck Thuny, MD,* Jean-François Avierinos, MD,* Geneviève Derumeaux, MD,† Lionel Beck, MD,* Christine Medail, MD,* Frederic Franceschi, MD,* Sebastien Renard, MD,* Ange Ferracci, MD,* Jean Lefevre, MD,* Roger Luccioni, MD, FACC,* Jean-Claude Deharo, MD,* Pierre Djiane, MD*

Marseille and Lyon, France

OBJECTIVES To compare the incidence of diastolic and systolic asynchrony, assessed by tissue Doppler imaging (TDI), in patients with congestive heart failure (CHF) and severe left ventricular (LV) dysfunction, and to assess TDI changes induced by cardiac resynchronization therapy (CRT).

BACKGROUND Thirty percent of CRT candidates are nonresponders. Besides QRS width, the presence of echographic systolic asynchrony has been used to identify future responders. Little is known about diastolic asynchrony and its change after CRT.

METHODS Tissue Doppler imaging was performed in 116 CHF patients (LV ejection fraction 26 ± 8%). Systolic and diastolic asynchrony was calculated using TDI recordings of right ventricular and LV walls.

RESULTS The CHF group consisted of 116 patients. Diastolic asynchrony was more frequent than systolic, concerning both intraventricular (58% vs. 47%; $p = 0.0004$) and interventricular (72 vs. 45%; $p < 0.0001$) asynchrony. Systolic and diastolic asynchrony were both present in 41% patients, but one-third had isolated diastolic asynchrony. Although diastolic delays increased with QRS duration, 42% patients with narrow QRS presented with diastolic asynchrony. Conversely, 27% patients with large QRS had no diastolic asynchrony. Forty-two patients underwent CRT. Incidence of systolic intraventricular asynchrony decreased from 71% to 33% after CRT ($p < 0.0001$), but diastolic asynchrony decreased only from 81% to 55% ($p < 0.0002$). Cardiac resynchronization therapy induced new diastolic asynchrony in eight patients.

CONCLUSIONS Diastolic asynchrony is weakly correlated with QRS duration, is more frequent than systolic asynchrony, and may be observed alone. Diastolic asynchrony is less improved by CRT than systolic. Persistent diastolic asynchrony may explain some cases of lack of improvement after CRT despite good systolic resynchronization. (J Am Coll Cardiol 2005;46:2250–7) © 2005 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) is now an accepted treatment of patients with drug-refractory congestive heart failure (CHF) (1). Widened QRS is considered as the landmark of cardiac asynchrony and this criterion has been used in most controlled studies on CRT (1,2). In addition, QRS width ≥130 ms is used in current American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology (ACC/AHA/NASPE) guidelines for biventricular pacemaker implantation (3). However, QRS width has been shown to be a weak predictor of clinical or echocardiographic improvement (4,5) and recent studies suggest that the presence of a systolic asynchrony as determined by tissue Doppler imaging (TDI) may have the potential to better identify future responders to CRT (6–8).

A number of systolic mechanical indices of asynchrony have been proposed, either between the left and the right ventricles (interventricular asynchrony) (9) or between the left ventricular (LV) walls (intraventricular asynchrony) (10–15). Most of these studies focused only on systolic synchronicity, whereas little is known about the existence of diastolic asynchrony.

Diastolic function plays a major role in symptoms and pathophysiology of CHF (16) and left bundle branch block (LBBB) has been shown to shorten LV diastolic filling time (17), to directly impair diastolic function (18–20), and to cause diastolic as well as systolic asynchrony (17). In addition, ventricular interaction in diastole has been described in one-half of patients with CHF, especially in those with increased LV filling pressures (21). Finally, the mechanisms responsible for the benefits of CRT in CHF patients are not

From the *Echocardiography Laboratory, La Timone Hospital, Marseille, France; and the †Hôpital Louis Pradel, Lyon, France.

Manuscript received October 31, 2004; revised manuscript received January 12, 2005, accepted February 14, 2005.

Abbreviations and Acronyms

CHF = congestive heart failure
CRT = cardiac resynchronization therapy
LBBB = left bundle branch block
LVEF = left ventricular ejection fraction
TDI = tissue Doppler imaging

fully understood. Systolic resynchronization probably explains in part the benefit derived from CRT, but other mechanisms, such as reduction of mitral regurgitation and improved diastolic filling, are probably also involved (22). However, no data exists concerning the role of diastolic resynchronization in these patients.

For these reasons, we performed a prospective study whose objectives were: 1) to compare the respective incidence of diastolic and systolic asynchrony, assessed by TDI, in a large population of patients with CHF with or without LBBB; and 2) to assess CRT-induced changes of systolic and diastolic asynchrony parameters in a population of patients with LBBB.

PATIENTS AND METHODS

Patients. Baseline characteristics of the populations are summarized in Table 1.

CHF POPULATION. One hundred sixteen consecutive patients with LV dysfunction (mean left ventricular ejection fraction [LVEF] 26 ± 8%; left ventricular end-diastolic diameter [LVEDD] 73 ± 9 mm) were included, regardless of QRS duration (mean duration 132 ± 43 ms) or New York Heart Association (NYHA) functional class. The population was divided into three groups according to QRS duration: group 1, QRS <120 ms (n = 40); group 2, QRS 120 to 150 ms (n = 34); and group 3, QRS >150 ms (n = 42).

CRT POPULATION. Forty-two patients (out of the CHF population) underwent CRT. All patients had drug-refractory heart failure (NYHA functional class III or IV), severe LV dysfunction (LVEF 26 ± 7%; LVEDD 73 ± 9 mm), and QRS enlargement on the surface electrocardiogram (mean duration 168 ± 34 ms). Only patients with sinus rhythm were included, although five patients had a history of paroxysmal or persistent AF but were in sinus rhythm at the time of implantation and of echocardiographic examination. The presence of echocardiographic asynchrony was not an inclusion criterion. CRT patients were similar to CHF group 3 patients in QRS duration (168 ± 34 ms vs. 177 ± 17 ms, respectively; p = 0.08) and mean ejection fraction (26 ± 7% vs. 27 ± 7%, respectively; p = 0.8). However, only 18 (43%) CHF group 3 patients were in NYHA functional class III or IV (mean NYHA functional class 2.6 ± 0.8 vs. 3.4 ± 0.5 in CRT patients; p < 0.0001).

IMPLANTATION OF BIVENTRICULAR PACEMAKER. Biventricular pacemakers were implanted as previously described (23). The LV pacing lead was inserted by transvenous approach through the coronary sinus into the lateral or posterolateral cardiac vein. The biventricular devices used in patients with sinus rhythm were InSync III (Medtronic, Minneapolis, Minnesota) in 35 patients and biventricular cardioverter defibrillator Contak CD (Guidant, Minneapolis, Minnesota) in 7 patients. After implantation, the atrioventricular interval was optimized to obtain the maximal diastolic filling time without interruption of the A wave using pulsed Doppler analysis of the transmitral flow ac-

Table 1. Baseline Characteristics of Study Groups

Variable	Controls (n = 40)	CHF Patients (n = 116)	CRT Patients (n = 42)
Clinical data			
Gender (male)	32 (80%)	91 (78%)	33 (79%)
Age (yrs)	60 ± 11	61 ± 14	58 ± 13
NYHA functional class		2.6 ± 0.9	3.4 ± 0.5
Ischemic cardiomyopathy		32 (28%)	14 (33%)
Nonischemic cardiomyopathy*		84 (72%)	28 (67%)
Diuretics		110 (95%)	42 (100%)
ACE inhibitors		107 (92%)	41 (98%)
Beta-blockers		89 (77%)	39 (93%)
Spironolactone		50 (43%)	22 (52%)
Electrocardiographic data			
QRS width (ms)	85 ± 13	132 ± 43	168 ± 34
PR interval (ms)	136 ± 13	161 ± 18	177 ± 38
Sinus rhythm	40 (100%)	97 (84%)	42 (100%)
Atrial fibrillation		19 (16%)	
Standard echo data			
Ejection fraction (%)	73 ± 6	26 ± 8	26 ± 7
LVEDD (mm)		73 ± 9	73 ± 9

*71 idiopathic, 5 chemotherapy induced, 4 valvular, 3 alcoholic, 1 postpartum cardiomyopathy. Data are presented as the mean value ± SD or as the number (percentage) of controls or patients.

ACE = angiotensin-converting enzyme; CHF = congestive heart failure; CRT = cardiac resynchronization therapy; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association.

JACC Vol. 46, No. 12, 2005
December 20, 2005:2250–7

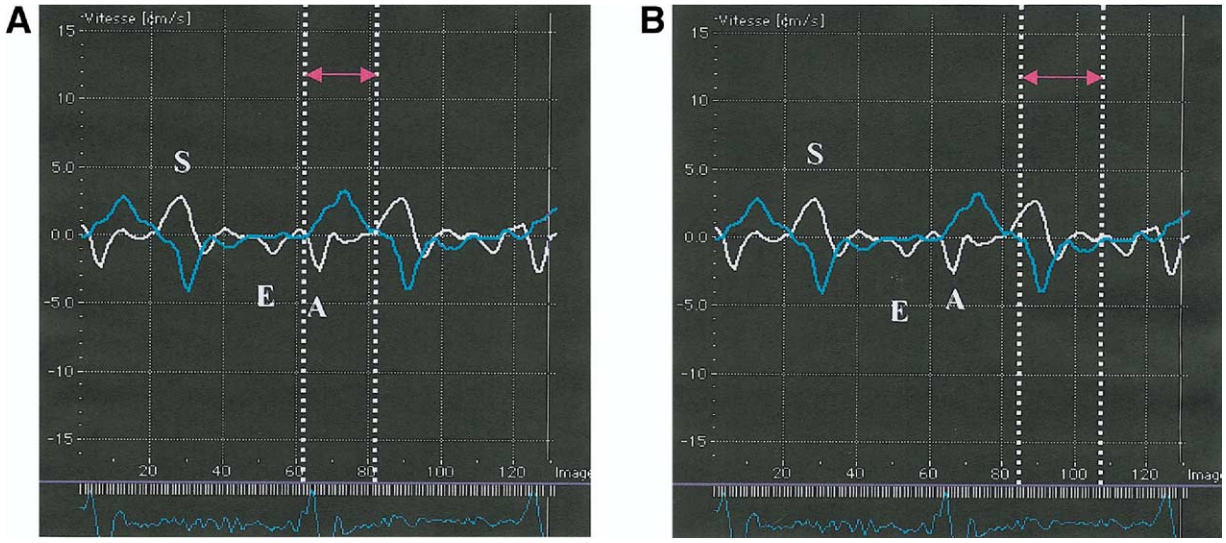

Figure 1. Methods of measurements of systolic and diastolic delays. **(A)** Measurement of systolic intraventricular delay. Tissue Doppler imaging recordings of the velocity curves of the septal wall **(blue curve)** and of the lateral wall **(white curve)** in a patient with severe systolic intraventricular asynchrony. The onset of each systolic velocity curve is used for measurement of systolic electromechanical delays of each ventricular wall **(dotted lines)**. A systolic intraventricular delay of 95 ms between these two walls is calculated **(pink arrow)**. **(B)** Similar measurements are performed for measurement of diastolic intraventricular delay in the same patient. The onset of each diastolic velocity curve is used for measurement of diastolic electromechanical delays of each ventricular wall **(dotted lines)**. A diastolic intraventricular delay of 115 ms between these two walls is calculated **(pink arrow)**.

cording to Ritter et al. (24). All biventricular devices were programmed to deliver simultaneous pacing of the right and left ventricle.

Echocardiographic protocol. Standard measurements, including Doppler parameters, were performed using a System Five ultrasound system (GE Vingmed Ultrasound, Horten, Norway) with a 3-MHz phased array probe. LV systolic and diastolic dimensions were measured by two-dimensional guided M-mode method. Ejection fraction was assessed by Simpson's rule using conventional apical four- and two-chamber views. Time velocity integral and duration of ejection were measured on the aortic Doppler signal. Diastolic function was evaluated on the transmitral Doppler signal (peak E and A, E/A ratio, diastolic filling time).

The TDI recordings were acquired during end-expiratory apnea in the apical four- and two-chamber views to assess the long-axis motion of the ventricles. Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation. Sector size and depth were optimized for the highest frame rate. Care was taken to keep the incidence angle between the direction of the Doppler beam and the analyzed vector of myocardial motion as small as possible. At least three consecutive beats were digitized. In the CRT population, measurements were performed the day after implantation, at baseline (pacemaker turned off), and after at least 10 min of biventricular pacing. All TDI recordings were performed by the same two authors.

DATA ANALYSIS. Regional myocardial pulsed-Doppler velocity profiles were reconstituted and computer analyzed offline (EchoPac 6.3.6; GE Vingmed Ultrasound) by positioning the sample volume in the middle of the basal portion of four different LV wall segments (septal, lateral, anterior, and inferior) and in the basal lateral right ventricular (RV) segment. With use of the QRS as a reference point, the systolic electromechanical delay (EMD) was measured as the time to the onset of the systolic velocity curve. Similarly, diastolic EMDs were obtained using the onset of the diastolic E-wave (Fig. 1). The average of at least three consecutive beats was used for comparison. Interventricular (inter-V) asynchrony was calculated as the difference between the systolic or diastolic EMDs of the lateral free wall of the right ventricle and of the most delayed LV segment. Intraventricular (intra-LV) asynchrony was defined as the time difference between the shortest and longest EMD among the four LV walls. A combined index of asynchrony was calculated as the sum of interventricular and intraventricular delays (7).

Statistical analysis. All data are expressed as mean value ± SD. Comparisons of data were performed using the Student *t* test for paired and unpaired data when appropriate. Linear regression analysis was used to calculate the correlation between electrical and echocardiographic parameters. A value of $p < 0.05$ was considered statistically significant.

To minimize the variability of the measurements, all TDI recordings were analyzed by the same author. The intraobserver variability assessed in 10 consecutive patients was 4.3% for diastolic intra-LV, 4.1% for diastolic inter-V, 4.4% for systolic intra-LV, and 4.0% for systolic inter-V delays.

Finally, systolic and diastolic asynchrony indices were evaluated in a control group of 40 healthy control subjects (32 men, 8 women; mean age 56 ± 15 years) with no history of cardiovascular disease in order to define threshold values for the different asynchrony parameters. They had normal physical, electrocardiographic, and standard echocardiographic examination (LVEF 73 ± 6%; QRS duration 85 ± 13 ms). Asynchrony delays obtained in the control popula-

Table 2. Systolic and Diastolic Interventricular and Intraventricular Delays (ms) in Controls, in the CHF Population According to QRS Duration, and in the CRT Population at Baseline and During Biventricular Stimulation

	Systolic Intra	Systolic Inter	Sum Systolic	Diastolic Intra	Diastolic Inter	Sum Diastolic
Control (n = 40)	17.4 ± 9.1	12.5 ± 11.5	29.9 ± 15	16.6 ± 9.4	13.3 ± 11.2	29.9 ± 14.8
CHF (n = 108)						
Group 1 (n = 36)	35 ± 29	30 ± 26	66 ± 51	39 ± 28	53 ± 39	92 ± 55
Group 2 (n = 32)	47 ± 43	44 ± 38	90 ± 74	55 ± 51	68 ± 50	123 ± 82
Group 3 (n = 40)	60 ± 51	62 ± 44	122 ± 79	76 ± 50	95 ± 59	171 ± 89
All patients (n = 108)	48 ± 44	46 ± 39	94 ± 73	58 ± 47	73 ± 53	131 ± 84
CRT (n = 42)						
Basal	73 ± 42	63 ± 51	137 ± 82	101 ± 91	89 ± 69	190 ± 135
Biv stimulation	36 ± 34	30 ± 33	66 ± 61	75 ± 60	66 ± 42	141 ± 93
p (baseline vs. Biv stimulation)	<0.0001	<0.0001	<0.0001	0.02	0.07	0.02

Biv = biventricular; Inter = interventricular; Intra = intraventricular; other abbreviations as in Table 1.

tion were used to characterize the range of normal intra-LV and inter-V delays for diastolic and systolic asynchrony. Gaussian's distribution of the control variables was verified by the Shapiro and Wilk test. The statistical alpha risk was fixed at 0.05, so that 95% of the control group was included in the mean ± 2 SD range. Values above the "mean + 2 SD" limit were considered statistically different from the control groups' value and classified as significant asynchrony.

RESULTS

One hundred eight patients (93%) in the CHF population had complete TDI analysis. Incomplete data were due to very low velocity profiles or to technical problems. In the CRT population, biventricular pacemaker implantation was successful in all patients. TDI recordings were adequate for analysis in all patients as well as in the control population.

Control population and definition of threshold values. Interventricular and intraventricular systolic and diastolic delays obtained in the control group are presented in Table 2, as well as values for the combined interventricular plus intraventricular index. Threshold values for significant asynchrony were 36 and 35 ms for systolic interventricular and intraventricular delays, respectively, and 35 and 36 ms for diastolic interventricular and intraventricular delays, respectively. Therefore, a delay exceeding 40 ms was used to define systolic and diastolic interventricular and intraventricular asynchrony. Similarly, a threshold value of 80 ms was used for the combined index (sum of inter- and intraventricular delays).

CHF population. ELECTROMECHANICAL TDI DELAYS. The analysis of electromechanical TDI delays showed that among patients displaying significant systolic intra-LV asynchrony, the lateral wall was the most delayed in 66%, the inferior wall in 15%, the anterior wall in 15%, and the septal wall in 4% of patients. For diastolic intra-LV asynchrony, the distribution was 62%, 16%, 17%, and 5% respectively.

RELATIVE INCIDENCE OF SYSTOLIC AND DIASTOLIC ASYNCHRONY. Diastolic intra- and interventricular delays were significantly longer than systolic delays (intra: $p = 0.04$; inter: $p < 0.0001$; sum inter+intra: $p = 0.0002$) (Table 2). Moreover, using the pre-defined thresholds for significant asynchrony, the incidence of diastolic asynchrony was higher than the incidence of systolic asynchrony for all parameters (Table 3) (intra: $p = 0.0004$; inter: $p < 0.0001$; sum inter+intra: $p < 0.0001$). Figure 2 shows the repartition of systolic and diastolic asynchrony in the CHF population. Among patients with CHF, 41% presented with both systolic and diastolic asynchrony, one-third had isolated diastolic asynchrony, and very few (8%) had isolated systolic asynchrony.

INCIDENCE OF ASYNCHRONY ACCORDING TO QRS DURATION. Table 2 displays inter- and intraventricular delays according to QRS duration. Both systolic and diastolic interventricular and intraventricular delays increased with increasing

Table 3. Percentage of Patients With Systolic and Diastolic Interventricular and Intraventricular Asynchrony in Controls, in the CHF Population According to QRS Duration, and in the CRT Population at Baseline and During Biventricular Stimulation

	Systolic Intra	Systolic Inter	Sum Systolic	Diastolic Intra	Diastolic Inter	Sum Diastolic
Control (n = 40)	0	0	0	0	0	0
CHF (n = 108)						
Group 1 (n = 36)	33	28	31	42	61	61
Group 2 (n = 32)	50	44	44	59	75	78
Group 3 (n = 40)	58	63	70	73	80	80
All patients (n = 108)	47	45	49	58	72	73
CRT (n = 42)						
Baseline	71	60	69	81	76	84
Biv stimulation	33	31	31	55	55	64
p (baseline vs. Biv stimulation)	<0.0001	<0.0001	<0.0001	0.0002	0.002	0.002

Abbreviations as in Tables 1 and 2.

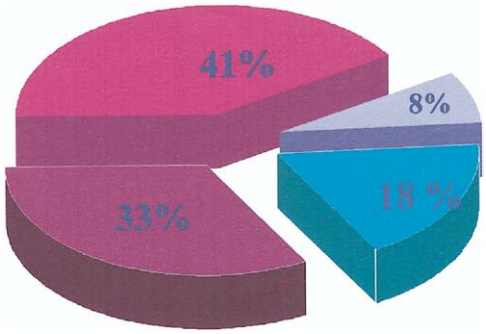

Figure 2. Relative incidence of systolic and diastolic asynchrony in the congestive heart failure population. **Purple** = diastolic only; **pink** = systolic and diastolic; **light blue** = systolic only; **blue** = no dyssynchrony.

QRS duration. However, both systolic and diastolic delays were weakly correlated with QRS duration (systolic intra: $r = 0.29$; $p < 0.002$; inter: $r = 0.33$; $p < 0.0001$; sum intra+inter: $r = 0.41$; $p < 0.0001$; diastolic intra: $r = 0.37$; $p < 0.0001$; inter: $r = 0.32$; $p = 0.0008$; sum intra+inter: $r = 0.41$; $p < 0.0001$).

Similarly, the number of patients with significant asynchrony increased with QRS duration (Table 3, Fig. 3). However, as shown in Figure 3, a significant number of patients with narrow QRS (group 1) displayed echocardiographic intraventricular asynchrony; one-third of these patients had significant asynchrony during systole and even more during diastole. Conversely, some patients with very large QRS (group 3) had no mechanical asynchrony. Forty-two percent of these patients did not present with systolic asynchrony, and 27% had no diastolic asynchrony despite the presence of typical LBBB on the surface electrocardiogram.

CRT population. ELECTROCARDIOGRAPHY. QRS duration significantly shortened from 168 ± 34 ms to 118 ± 23 ms after CRT ($p < 0.0001$). The PR interval was reduced from 177 ± 38 ms to 134 ± 15 ms ($p < 0.0001$). Heart rate was not significantly different between baseline and CRT (69.7 ± 12 vs. 70 ± 6; $p = 0.74$).

STANDARD ECHOCARDIOGRAPHY. Ejection fraction did not improve significantly after biventricular pacing (26.8 ± 7.4% vs 27.4 ± 7.4%; $p = 0.1$). Aortic velocity time integral (11.1 ± 2.1 cm vs. 12.8 ± 2.3 cm; $p < 0.0001$) and duration of the ejection period (247 ± 52 ms vs. 269 ± 56 ms; $p < 0.0001$) increased significantly. Diastolic E- and A-wave velocities were not significantly different between baseline and CRT mode (86 ± 32 cm/s vs. 81 ± 29 cm/s; $p = 0.2$; and 63 ± 31 cm/s vs. 65 ± 33 cm/s; $p = 0.6$). LV diastolic filling time (319 ± 80 vs. 396 ± 89; $p < 0.0001$) and deceleration time (186 ± 41 vs. 200 ± 53; $p < 0.0001$) increased after pacing.

ASYNCHRONY PARAMETERS (TABLE 2). All systolic intra- and interventricular delays were significantly reduced after CRT. Diastolic delays were less improved than systolic delays. The incidence of diastolic asynchrony remained high during biventricular pacing (Table 3, Fig. 4). Nearly one-third of the patients still displayed systolic asynchrony, and more than half still had diastolic asynchrony. In 11 patients without intra-LV asynchrony at baseline, CRT induced de novo asynchrony: in 3 patients during systole and in 8 during diastole (mean increase in delays 64 and 76 ms, respectively).

There was no significant correlation between QRS shortening after CRT and the improvement of any of the systolic or diastolic asynchrony parameters. Similarly, no correlation was found between PR interval reduction and the improvement of diastolic intra- or interventricular asynchrony ($p = 0.62$ and 0.69, respectively).

Finally, there was no significant difference between "TDI responders" (suppression of significant systolic and diastolic asynchrony) and "TDI nonresponders" during CRT concerning the benefit in terms of EF (27.5 ± 6% vs. 27.3 ± 7%; $p = 0.4$), aortic velocity time integral (12.9 ± 2.4 cm vs. 12.6 ± 2.2 cm; $p = 0.2$) or diastolic filling time (379 ± 76 ms vs. 416 ± 82 ms; $p = 0.09$) in this acute study. The programmed AV delay was similar between TDI responders and nonresponders (106.4 ± 19 ms vs. 105.5 ± 20 ms; $p = 0.5$).

OPTIMIZATION OF THE VV-DELAY. Optimization of the VV-delay was performed under echocardiographic and TDI guidance in a subgroup of 15 patients in whom resynchronization was judged unsatisfactory by post-implantation TDI study. The main objective of this adjustment was to

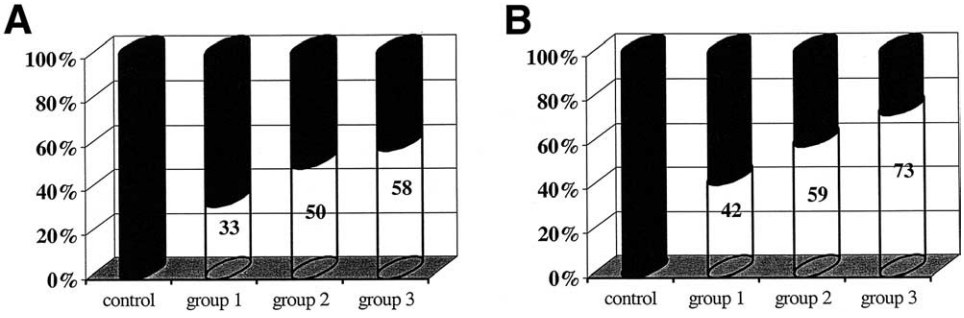

Figure 3. Incidence of significant systolic and diastolic intraventricular asynchrony according to QRS duration in the CHF population (n = 108). **(A)** Incidence of systolic asynchrony. **(B)** Incidence of diastolic asynchrony. The **white bars** represent the relative proportion of patients with asynchrony in each group.

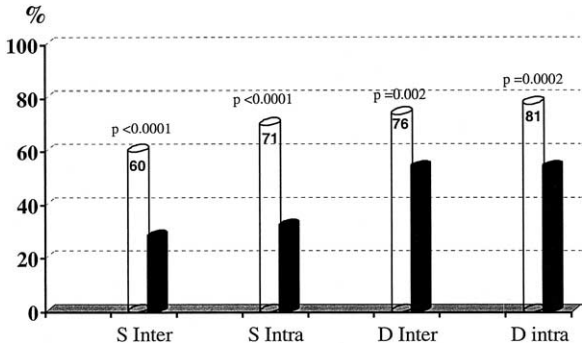

Figure 4. Incidence of systolic (S) and diastolic (D) intraventricular and interventricular asynchrony at baseline **(white bars)** and under biventricular pacing **(black bars)** in the cardiac resynchronization therapy population (42 patients).

obtain the shortest systolic delays. In this subgroup, the incidences of persistent systolic and diastolic intraventricular asynchronies were 54% and 74% after implantation, respectively. These incidences decreased to 27% and 47%, respectively, after VV-delay optimization. In no case was VV-delay optimization responsible for a worsening of diastolic asynchrony.

Influence of underlying disease and diastolic dysfunction. Subgroup analysis showed no differences concerning asynchrony parameters between dilated and ischemic cardiomyopathies or between patients in sinus rhythm or with atrial fibrillation. Similarly, no correlation was found between diastolic delays evaluated by TDI and standard Doppler parameters of diastolic function (E/A ratio, deceleration time, diastolic filling time).

DISCUSSION

The main results of this study are as follows:

1. Diastolic asynchrony is frequently observed by TDI in patients with dilated cardiomyopathy and is weakly correlated with QRS duration.
2. Diastolic is more frequent than systolic asynchrony in these patients and may be observed alone.
3. Diastolic asynchrony is less improved by CRT than systolic asynchrony.

Echocardiographic evaluation of cardiac resynchronization therapy. Although a QRS duration ≥130 ms is part of the ACC/AHA/NASPE guidelines for implantation of pacemakers and antiarrhythmic devices (3), 20% to 30% of patients do not respond to CRT (5,8) and convincing evidence exists that asynchrony may be absent in patients with large QRS (25) or present in patients with narrow QRS (26).

Various echocardiographic approaches have been proposed to evaluate mechanical asynchrony and select future responders to CRT, including M-mode echocardiography (10), automatic endocardial LV border detection (11), measurement of time difference between left and right pre-ejection intervals (9), as well as several TDI methods (12–15,25–27). However, none of the proposed asynchrony parameters has been validated in a large controlled trial and thus should be used in clinical practice for patient selection. Tissue Doppler imaging was the most frequently used technique in past studies. The rationale for using TDI techniques includes the fact that pulsed-wave TDI has a high sampling rate, resulting in a high temporal resolution with the potential to investigate cardiac episodes of short duration, and that it has been shown to be accurate to assess regional timing of not only systolic but also diastolic cardiac events (14). However, these studies suffer from several limitations: First, they used different TDI modes, some authors measuring delays on myocardial velocity curves ("live" measurements of myocardial velocities by pulsed-wave TDI [6,15,27]), others using off-line analysis of TDI tracings derived by post-processing of the velocity curves (11–15,25,26), and other authors using TDI curves to derive strain and strain rate (28) or tissue tracking; second, the method of measurement of EMDs varies among studies, some authors using the time difference between QRS and the onset of the systolic velocity curve (26) and others using the peak velocity (26); finally, different definitions of what a significant asynchrony is have been reported (14,25,27) and no consensus exists on this point.

In our study, both interventricular and intraventricular delays were obtained from off-line analysis of TDI recordings. Using a validation against a control population, a systolic or diastolic delay ≥40 ms was considered significant for both interventricular and intraventricular asynchrony. Moreover, a combined index (sum of systolic and diastolic delays) ≥80 ms was also considered significant.

Diastolic versus systolic asynchrony. Although several studies focused on systolic asynchrony, data concerning diastolic asynchrony are very scarce. However, diastolic phenomena are probably as important as systolic in CRT.

First, several echocardiographic studies demonstrated that LBBB causes marked diastolic function impairment both in CHF patients (18,19) and in patients with normal systolic function (17,20). Main diastolic abnormalities caused by LBBB included reduced LV filling time, prolonged isovolumic contraction and relaxation times, altered transmitral filling patterns, and prolonged duration of mitral regurgitation in patients with LV dysfunction. Morris-Thurgood et al. (29) found diastolic filling abnormalities to be of crucial importance in CRT patients and proposed that part of the benefit of CRT was probably related to better LV filling rather than ventricular systolic resynchronization (29).

Second, ventricular interaction in diastole also plays a potential role in CHF patients. Atherton et al. (21) documented that LV filling was impeded in one-half of CHF patients by ventricular interaction in diastole from the raised RV diastolic pressure and by external constraint from the pericardium, especially in patients with increased LV filling pressure. This diastolic interaction could explain the delayed onset of mechanical diastolic motion in the LV (measured by TDI), even in patients without systolic interventricular

asynchrony. The reduction of the ventricular interaction in diastole during LV pacing has also been proposed to be the dominant mechanism by which LV pacing may produce hemodynamic improvement in CHF patients (29,30).

Third, very few data exist concerning diastolic asynchrony itself (14,31). However, it has been shown for a long time that LBBB caused both systolic and diastolic asynchronies (17). More recently, in their study of 112 CHF patients, Yu et al. (14) found the incidence of systolic and diastolic asynchrony to be 51% and 46%, respectively, in patients with narrow QRS, and 73% and 69%, respectively, in patients with large QRS.

In our study, diastolic delays were significantly longer than systolic delays, and the incidence of diastolic asynchrony was higher than that of systolic asynchrony concerning both intra-LV (58% vs. 47%) and inter-V (72% vs. 45%) asynchrony. In a majority of CHF patients in our study, diastolic and systolic asynchronies were both present. This may be explained by the fact that diastole and systole are closely linked: A delayed contraction of a segment will result in a delayed relaxation in this segment. However, the main result of our study is that diastolic asynchrony was more frequently observed than systolic asynchrony. The reasons why diastolic is more frequent than systolic asynchrony are not clear. The length of diastole, which includes both isovolumic relaxation and contraction times, may make diastolic study more sensitive than systolic and allow an earlier identification of a delayed segment, before systolic asynchrony occurs. This was illustrated by the fact that diastolic asynchrony was observed alone in more than one-third of CHF patients in our study.

Finally, the lack of correlation between parameters of diastolic asynchrony and conventional Doppler parameters of diastolic function (E/A ratio, deceleration time, and LV diastolic filling time) may be explained by the fact that the latter parameters are highly dependent on LV filling pressure (which may vary widely in patients with CHF) and do not reflect only the diastolic coordination between LV walls.

Mechanical versus electrical asynchrony. Another important result of our study is that although both interventricular and intraventricular delays increased with increasing QRS duration, the correlation between mechanical and electrical asynchrony was weak. Interestingly, the best correlation was observed for the combination of intraventricular and interventricular asynchrony (7). Moreover, a significant number of patients with large QRS presented without significant echocardiographic dyssynchrony. Conversely, one-third of patients with narrow QRS presented with systolic and even more (61%) with diastolic asynchrony. These results are in agreement with those of Yu et al. (14), who found intraventricular asynchrony in only 73% patients with wide QRS, but also in 51% patients with narrow QRS. Similarly, Ghio et al. (25), using a delay of >50 ms to define intraventricular asynchrony, found a significant systolic asynchrony in 29.5% of patients with narrow QRS and in 71% of patients with large QRS. Our study not only confirmed these data but also showed that these results may be applicable to diastolic asynchrony.

Influence of CRT. Several studies showed that CRT was associated with a shortening of inter- and intraventricular systolic delays. For example, interventricular delay, as measured by pulsed Doppler, was reduced by 19% after CRT in the Multicenter Insync Randomized Clinical Evaluation (MIRACLE) study (2). Similarly, systolic intraventricular resynchronization has been demonstrated after CRT using both M-mode echocardiography (10) and TDI techniques (6). More important, Penicka et al. (7), in a series of 49 patients studied by TDI before CRT, showed that the combination of intraventricular and interventricular asynchrony was the best predictor of LV functional recovery after CRT.

However, no study focused on the influence of CRT on diastolic resynchronization. In our study, CRT was associated with a significant reduction of QRS width and systolic as well as diastolic delays. However, diastolic asynchrony was less improved by CRT than systolic. Moreover, in some patients, CRT was associated with worsening or new occurrence of systolic and/or diastolic asynchrony. Finally, optimization of the VV delay was performed under echocardiographic guidance in a subgroup of patients with unsatisfactory resynchronization and allowed a further decrease of the incidence of both systolic and diastolic asynchrony in these patients. These results underline the need to perform systematic measurements of both systolic and diastolic delays before and after CRT, and to try to optimize VV delay when resynchronization is judged unsatisfactory by post-implantation echographic study.

Besides resynchronization of the ventricles, another potential benefit of CRT in CHF may be related to the improvement of atrioventricular (AV) synchrony. The AV time delay has the potential to influence chamber mechanics and cardiac output (5) and to affect cardiac filling. In our series, all patients underwent AV delay optimization after pacemaker implantation. However, although DDD pacing alone may improve AV asynchrony, it frequently results in a worsening of both interventricular and intraventricular synchrony; moreover, the benefits of LV pacing in patients with CHF and chronic RV pacing seem comparable to those of CHF patients without RV pacing, suggesting that CRT acts through ventricular resynchronization rather than optimization of the AV delay (32). Thus, associated LV stimulation is preferable in case of LV dysfunction in order to ensure AV and intraventricular and interventricular synchronization (32). We further need to evaluate which type of asynchrony (diastolic, systolic, atrioventricular, or intraventricular or interventricular) should be given priority when programming biventricular pacemakers.

Study limitations. Some limitations of our study are inherent to the TDI technique. Seven percent of patients among the CHF population had to be excluded because of very low velocity profiles or technical problems. In addition, apart from active contraction, regional systolic velocities

may reflect passive motion due to heart motion or tethering by adjacent segments. Although we tried to minimize this effect by performing measurements during end-expiratory apnea, strain rate techniques would have been more precise to identify the true wall contraction. Finally, the TDI method is angle dependent and can only assess longitudinal contraction.

Another limitation of our study is the heterogeneity of the studied population, including both ischemic and idiopathic cardiomyopathy. Our study was an acute study, and the long-term significance of our results has to be evaluated by specific longitudinal studies.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Tissue Doppler imaging is a useful method for the assessment of systolic and diastolic asynchrony. Diastolic asynchrony is weakly correlated with QRS duration, is more frequent than systolic asynchrony, and may be observed alone in some patients. In addition, diastolic asynchrony is less improved by CRT than systolic asynchrony. Persistent diastolic asynchrony may explain in some cases the lack of clinical improvement after CRT despite good systolic resynchronization.

The prognostic value and clinical significance of diastolic asynchrony needs to be assessed in prospective longitudinal studies.

Reprint requests and correspondence: Prof. Gilbert Habib, Cardiology Department, Hôpital la Timone, Boulevard Jean Moulin, 13005 Marseille, France. E-mail: gilbert.habib@free.fr.

REFERENCES

1. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.
2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
3. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE—2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices. J Am Coll Cardiol 2002;40:1703–19.
4. Nelson GS, Curry CW, Wyman BT, et al. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000;101:2703–9.
5. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. J Am Coll Cardiol 2002;39:194–201.
6. Ansalone G, Giannantoni P, Ricci R, et al. Doppler myocardial imaging in patients with heart failure receiving biventricular pacing treatment. Am Heart J 2001;142:881–96.
7. Penicka, M, Bartunek J, De Bruyne B, et al. Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging echocardiography. Circulation 2004; 109:978–83.
8. Bax JJ, Marwick TH, Molhoek SG, et al. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. Am J Cardiol 2003;92:1238–40.
9. Rouleau F, Merheb M, Geffroy S, et al. Echocardiographic assessment of the interventricular delay of activation and correlation to the QRS width in dilated cardiomyopathy. Pacing Clin Electrophysiol 2001;24: 1500–6.
10. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol 2002;40:1615–22.
11. Breithardt OA, Stellbrink C, Kramer AP, et al. Echocardiographic quantification of left ventricular asynchrony predicts an acute hemodynamic benefit of cardiac resynchronization therapy. J Am Coll Cardiol 2002;40:536–45.
12. Bax JJ, Molhoek SG, van Erven L, et al. Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony before and after biventricular pacing in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2003;91:94–7.
13. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002;105:438–45.
14. Yu CM, Lin H, Zhang Q. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003;89:54–60.
15. Garrigue S, Reuter S, Labeque JN, et al. Usefulness of biventricular pacing in patients with congestive heart failure and right bundle branch block. Am J Cardiol 2001;88:1436–41.
16. Gaasch WH, Zile MR. Left ventricular diastolic dysfunction and diastolic heart failure. Annu Rev Med 2004;55:373–94.
17. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989;79:845–53.
18. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. Br Heart J 1991;66: 443–7.
19. Ozdemir K, Altunkeser BB, Korkut B, et al. Effect of left bundle branch block on systolic and diastolic function of left ventricle in heart failure. Angiology 2004;55:63–71.
20. Sadaniantz A, Saint Laurent L. Left ventricular Doppler diastolic filling patterns in patients with isolated left bundle branch block. Am J Cardiol 1998;81:643–5.
21. Atherton JJ, Morre TD, Lele SS, et al. Diastolic ventricular interaction in chronic heart failure. Lancet 1997;349:1720–4.
22. Bleasdale RA, Frenneaux MP. Cardiac resynchronisation therapy: when the drugs don't work. Heart 2004;90 Suppl VI:vi2–4.
23. Daubert JC, Ritter P, Le Breton H, et al. Permanent left ventricular pacing with transvenous leads inserted into the coronary veins. Pacing Clin Electrophysiol 1998;21:239–45.
24. Ritter P, Padeletti L, Gillio-Meina L, Gaggini G. Determination of the optimal atrioventricular delay in DDD pacing. Comparison between echo and peak endocardial acceleration measurements. Europace 1999;2:126–30.
25. Ghio S, Constantin C, Klersy C, et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. Eur Heart J 2004; 25:571–8.
26. Yu CM, Lin H, Zhang Q, et al. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003;89:54–60.
27. Bader H, Garrigue S, Lafitte S, et al. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. J Am Coll Cardiol 2004;43:248–56.
28. Sogaard P, Egeblad H, Kim WY, et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. J Am Coll Cardiol 2002;40:723–30.
29. Morris-Thurgood JA, Turner MS, Nightingale AK, et al. Pacing in heart failure: improved ventricular interaction in diastole rather than systolic re-synchronization. Europace 2000;2:271–5.
30. Bleasdale RA, Turner MS, Mumford CE, et al. Left ventricular pacing minimizes diastolic ventricular interaction, allowing improved preload-dependent systolic performance. Circulation 2004;110:2395–400.
31. Kang SJ, Song JK, Yang HS, et al. Systolic and diastolic regional myocardial motion of pacing-induced versus idiopathic left bundle branch block with and without left ventricular dysfunction. Am J Cardiol 2004;93:1243–6.
32. Leon AR, Greenberg JM, Kanuru N, et al. Cardiac resynchronisation in patients with congestive heart failure and chronic atrial fibrillation. Effect of upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol 2002;39:1258–63.